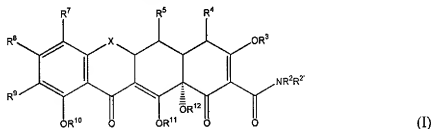


Amendments to the Claims

This listing of claims will replace all prior versions and listings of claims in the application:

1. **(Currently Amended)** A method for treating or preventing malaria in a subject, comprising administering to said subject an effective amount of a substituted tetracycline compound of formula I or a pharmaceutically acceptable salt thereof:



wherein:

- X is CR⁶R⁶;
- R² and R^{2'} are each hydrogen;
- R^{4'} and R^{4''} are each alkyl;
- R⁴ is NR^{4'}R^{4''};
- R³, R¹¹ and R¹² are each hydrogen;
- R¹⁰ is hydrogen;
- R⁵ is hydroxyl, hydrogen or thiol;
- R⁶ and R^{6'} are independently hydrogen, hydroxyl, thiol or alkyl;
- R⁷ is substituted or unsubstituted furanyl, substituted or unsubstituted benzofuranyl, substituted or unsubstituted thienyl or substituted or unsubstituted benzothienyl;
- R⁹ is hydrogen; and
- R⁸ is hydrogen; ~~and pharmaceutically acceptable salts thereof;~~ such that malaria is treated or prevented in said subject.

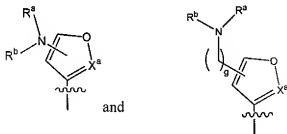
2. **(Canceled)**

3. **(Canceled)**

4. **(Previously Presented)** The method of claim 1, wherein R⁵, R⁶, and R^{6'} are each hydrogen.

5 - 28. **(Canceled)**

29. **(Currently Amended)** The method of claim 1, wherein R^7 is substituted furanyl or substituted thienyl.
30. **(Previously Presented)** The method of claim 29, wherein R^7 is substituted with halogen, alkoxy, amino, acyl, alkyl, nitro, formyl, amido, alkenyl, alkynyl, or aryl.
31. **(Previously Presented)** The method of claim 30, wherein R^7 is substituted with alkoxy and further wherein said alkoxy is methoxy, ethoxy, propoxy, methylene dioxy, or ethylene dioxy.
32. **(Previously Presented)** The method of claim 30, wherein R^7 is substituted with alkyl and further wherein said alkyl is substituted or unsubstituted methyl, ethyl, propyl, butyl or pentyl.
33. **(Previously Presented)** The method of claim 32, wherein said substituted methyl, ethyl, propyl, butyl or pentyl is substituted with an amino, carbocyclic or heterocyclic group.
34. **(Previously Presented)** The method of claim 30, wherein R^7 is substituted with acyl and further wherein said acyl is acetyl.
35. **(Previously Presented)** The method of claim 1, wherein R^7 is substituted or unsubstituted benzofuranyl or substituted or unsubstituted benzothieryl.
36. **(Previously Presented)** The method of claim 1, wherein R^7 is unsubstituted thienyl or unsubstituted furanyl.
- 37 – 41. **(Canceled)**
42. **(Previously Presented)** The method of claim 29, wherein said substituent comprises an ionizable nitrogen atom.
43. **(Previously Presented)** The method of claim 1, wherein R^7 is selected from the group consisting of:



wherein:

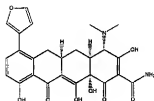
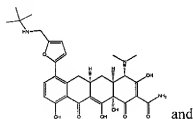
R^a and R^b are each independently hydrogen, halogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, or heterocyclic;

g is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20; and

X⁸ is substituted carbon.

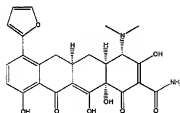
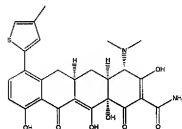
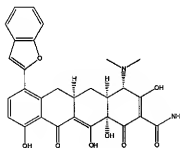
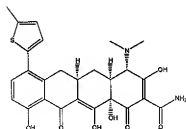
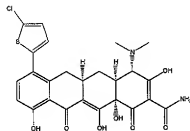
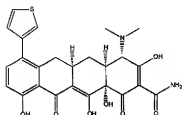
44 – 48. (Canceled)

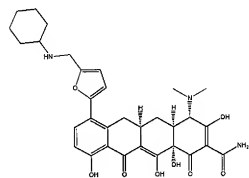
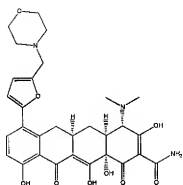
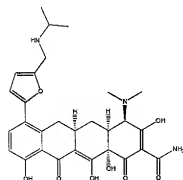
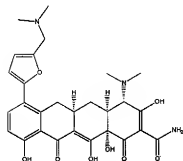
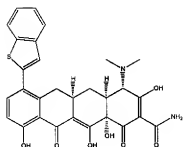
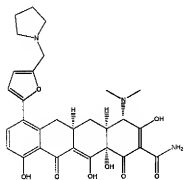
49. (Previously Presented) The method of claim 1, wherein said compound is selected from the group consisting of:

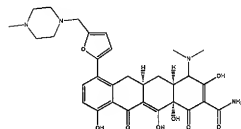
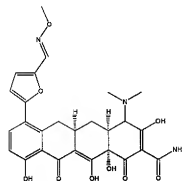
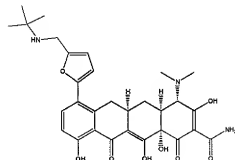
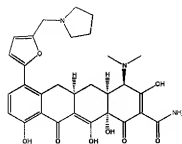
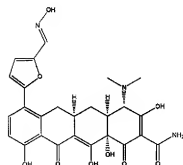
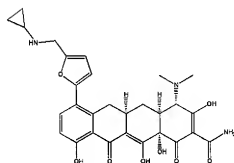
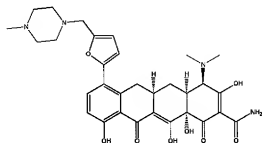
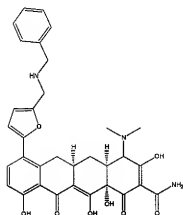


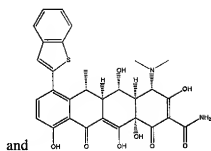
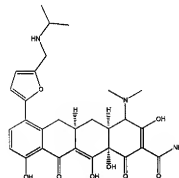
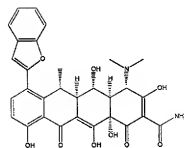
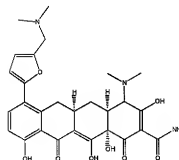
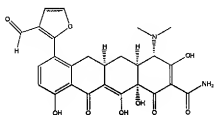
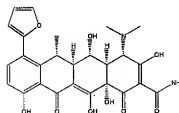
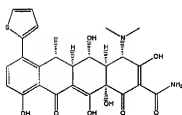
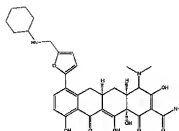
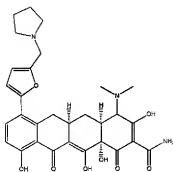
and

50. (Previously Presented) The method of claim 1, wherein said compound is selected from the group consisting of:





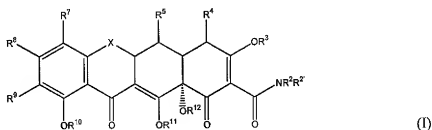




51. **(Original)** The method of claim 1, wherein said subject is a human.
52. **(Previously Presented)** The method of claim 1, wherein said substituted tetracycline compound has anti-gram positive microbial activity.
53. **(Previously Presented)** The method of claim 52, wherein said anti-gram positive microbial activity is greater than about 0.05 $\mu\text{g/ml}$.
54. **(Previously Presented)** The method of claim 53, wherein said anti-gram positive microbial activity is greater than about 5 $\mu\text{g/ml}$.
55. **(Previously Presented)** The method of claim 1, wherein said substituted tetracycline compound is non-antibacterial.
56. **(Original)** The method of claim 1, wherein said substituted tetracycline compound has a cytotoxicity of 25 $\mu\text{g/ml}$ or greater.
57. **(Original)** The method of claim 1, wherein said substituted tetracycline compound has a MIC of 150 nM or less.
58. **(Original)** The method of claim 57, wherein said substituted tetracycline compound has a MIC of 50 nM or less.
59. **(Original)** The method of claim 58, wherein said substituted tetracycline compound has a MIC of 10 nM or less.
60. **(Currently Amended)** The method of claim 59, wherein said substituted tetracycline compound has a MIC [[or]] of 5 nM or less.
61. **(Original)** The method of claim 1, wherein said malaria is caused by a plasmodium protozoan selected from the group consisting of: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*.
62. **(Currently Amended)** The method of claim 1, wherein said malaria is resistant to one or more anti-malarial compounds selected from the group consisting of: proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, pyronaridine~~[[.]]~~ and 1,16-hexadecamethylenebis(N-methylpyrrolidinium) dibromide.
- 63 – 65. **(Canceled)**
66. **(Currently Amended)** The method of claim 1, further comprising administering an anti-malarial compound selected from the group consisting of: proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone,

pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, ampyroquine, sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, pyronaridine, 1,16-hexadecamethylenebis(N-methylpyrrolidinium)dibromide[[,]] and combinations thereof.

67. **(Currently Amended)** A method for increasing the antimalarial activity of an antimalarial compound, comprising administering said antimalarial compound in combination with an effective amount of a substituted tetracycline compound, such that the antimalarial activity of said antimalarial compound is increased, wherein said tetracycline compound is of formula I or a pharmaceutically acceptable salt thereof:



wherein:

X is CR^{6'}R^{6'};

R² and R^{2'} are each hydrogen;

R^{4'} and R^{4''} are each alkyl;

R⁴ is NR^{4'}R^{4''};

R³, R¹¹ and R¹² are each hydrogen;

R¹⁰ is hydrogen;

R⁵ is hydroxyl, hydrogen or thiol;

R⁶ and R^{6'} are independently hydrogen, hydroxyl, thiol or alkyl;

R⁷ is substituted or unsubstituted furanyl, substituted or unsubstituted benzofuranyl, substituted or unsubstituted thienyl or substituted or unsubstituted benzothienyl;

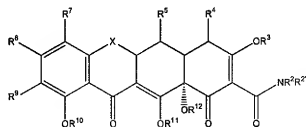
R⁹ is hydrogen; and

R⁸ is hydrogen; ~~and pharmaceutically acceptable salts thereof.~~

68. **(Currently Amended)** The method of claim 67, wherein said antimalarial compound is selected from the group consisting of: proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, ampyroquine,

sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, pyronaridine, 1,16-hexadecamethylenebis(N-methylpyrrolidinium)dibromide[[,]] and combinations thereof.

69. **(Currently Amended)** A method for preventing malaria in a mammal, comprising administering to said mammal an effective amount of a substituted tetracycline compound, such that malaria is prevented in said mammal, wherein said tetracycline compound is of formula I or a pharmaceutically acceptable salt thereof:



wherein:

X is CR^{6'}R⁶;

R² and R^{2'} are each hydrogen;

R^{4'} and R^{4''} are each alkyl;

R⁴ is NR^{4'}R^{4''};

R³, R¹¹ and R¹² are each hydrogen;

R¹⁰ is hydrogen;

R⁵ is hydroxyl, hydrogen or thiol;

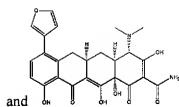
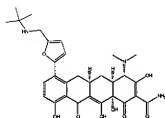
R⁶ and R^{6'} are independently hydrogen, hydroxyl, thiol or alkyl;

R⁷ is substituted or unsubstituted furanyl, substituted or unsubstituted benzofuranyl, substituted or unsubstituted thienyl or substituted or unsubstituted benzothieryl;

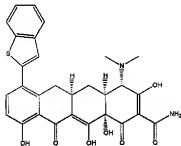
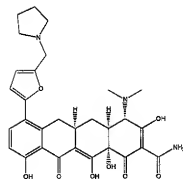
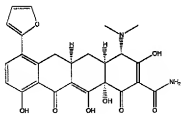
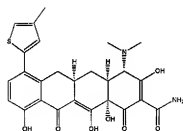
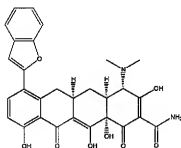
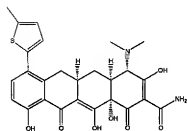
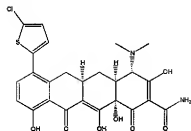
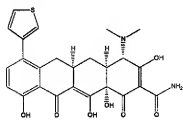
R⁹ is hydrogen; and

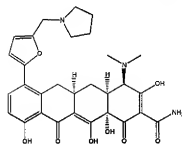
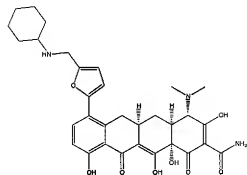
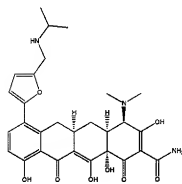
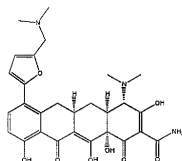
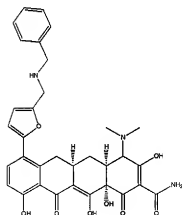
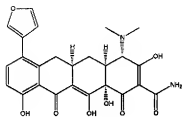
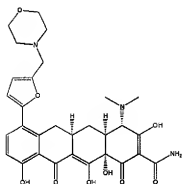
R⁸ is hydrogen; and pharmaceutically acceptable salts thereof.

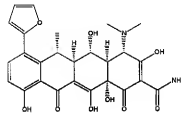
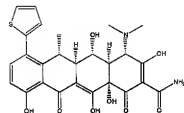
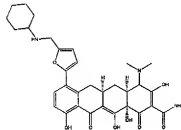
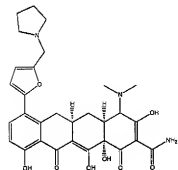
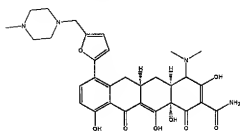
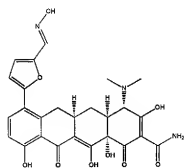
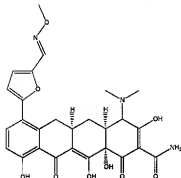
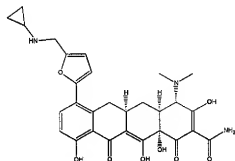
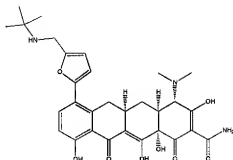
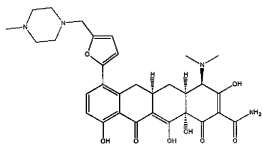
70. **(Previously Presented)** The method of claim 69, wherein said substituted tetracycline compound is selected from the group consisting of:

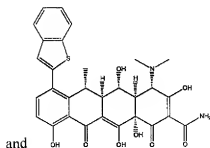
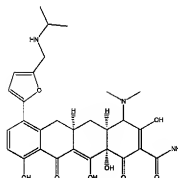
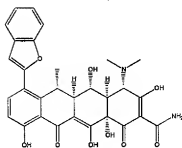
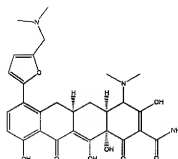
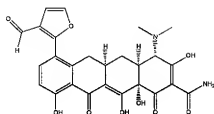


71. (Previously Presented) The method of claim 69, wherein said substituted tetracycline compound is selected from the group consisting of:









and

72. **(Previously Presented)** The method of claim 69, wherein said substituted tetracycline compound is non-antibacterial.

73. **(Previously Presented)** The method of claim 69, wherein said substituted tetracycline compound has anti-gram positive microbial activity.

74. **(Previously Presented)** The method of claim 73, wherein said anti-gram positive microbial activity is greater than about 0.05 $\mu\text{g/ml}$.

75. **(Previously Presented)** The method of claim 74, wherein said anti-gram positive microbial activity is greater than about 5 $\mu\text{g/ml}$.

76. **(Original)** The method of claim 75, wherein said substituted tetracycline compound has a cytotoxicity of 25 $\mu\text{g/ml}$ or greater.

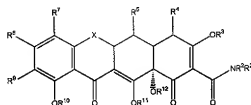
77. **(Previously Presented)** The method of claim 69, wherein said substituted tetracycline compound has a MIC of 150 nM or less.

78. **(Original)** The method of claim 77, wherein said substituted tetracycline compound has a MIC of 50 nM or less.

79. **(Original)** The method of claim 78, wherein said substituted tetracycline compound has a MIC of 10 nM or less.

80. **(Currently Amended)** The method of claim 79, wherein said substituted tetracycline compound has a MIC ~~[[or]]~~ of 5 nM or less.

81. **(Currently Amended)** A pharmaceutical composition comprising an effective amount of a substituted tetracycline compound to treat malaria in a mammal and a pharmaceutically acceptable carrier, wherein said tetracycline compound is of formula I or a pharmaceutically acceptable salt thereof:



(I)

wherein:

X is CR^{6'}R^{6''};

R² and R^{2'} are each hydrogen;

R^{4'} and R^{4''} are each alkyl;

R⁴ is NR^{4'}R^{4''};

R³, R¹¹ and R¹² are each hydrogen;

R¹⁰ is hydrogen;

R⁵ is hydroxyl, hydrogen or thiol;

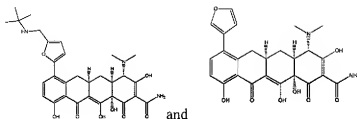
R⁶ and R^{6'} are independently hydrogen, hydroxyl, thiol or alkyl;

R⁷ is substituted or unsubstituted furanyl, substituted or unsubstituted benzofuranyl, substituted or unsubstituted thienyl or substituted or unsubstituted benzothienyl;

R⁹ is hydrogen; and

R⁸ is hydrogen; ~~and pharmaceutically acceptable salts thereof.~~

82. **(Previously Presented)** The pharmaceutical composition of claim 81, wherein said substituted tetracycline compound is selected from the group consisting of:



83. (Canceled)

84. (Currently Amended) The pharmaceutical composition of claim 81, further comprising a ~~secondary-agent~~ anti-malarial compound.

85. (Currently Amended) The pharmaceutical composition of claim 84, wherein the ~~secondary-agent~~ anti-malarial compound is selected from the group consisting of proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, 1,16-hexadecamethylenebis(N-methylpyrrolidinium)dibromide and pyronaridine.

86. (Canceled)

87. (Canceled)